

REMARKS

Claims 1-8, 24-35, 38 and 40-54 are presently pending. Claims 28-33 and 40-46 have been withdrawn from consideration as being drawn to a non-elected invention.

Attorneys for Applicants affirm the election made with traverse during the July 6, 2004 telephone conversation with the Examiner to prosecute the invention of Group I, claims 1-8, 24-27, 34-38 and 47-54, drawn to products.

Claims 1, 2 and 25 have been amended. Support for amended claims 1, 2 and 25 is found in the specification and claims 1, 2 and 25 as filed. *In re Driscoll*, 562 F.2d 1245 (C.C.P.A. 1977). Claims 8 and 24 have been amended to recite that the compositions can comprise a pharmaceutically acceptable diluent. Support for these amendments is found in the specification at page 23, lines 4-6. No new matter has been added.

Applicants reserve their right to prosecute the subject matter of any canceled claim, any amended claim, any withdrawn claim or any other unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications.¹

I. The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 36 and 37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for all the diseases or disorders listed in claim 36 (*e.g.*, all cancers). Without acquiescing to the rejection of claims 36 and 37 under 35 U.S.C. § 112, first paragraph, Applicants have canceled claims 36 and 37 without prejudice solely to expedite prosecution.

Accordingly, Applicants respectfully submit that the rejection of claims 36 and 37 under 35 U.S.C. § 112, first paragraph, is now moot and must be withdrawn.

II. The Rejection Under 35 U.S.C. § 102(b)

Claims 1, 2, 8, 24, 25 and 50 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Laakso *et al.* (CA 51:76969) (“Laakso”); Mosby *et al.* (CA 54:80551) (“Mosby”); Akamatsu (CA 58:27252) (“Akamatsu”); U.S. Patent No. 4,202,827 to Tzikas *et al.* (“Tzikas I”), GB 1,293,557 to Hoechst (“Hoechst”) and DE 1 257 149 to Neeff (“Neeff”).

¹ Applicants have not yet elected to cancel the unelected subject matter in anticipation of possible rejoinder.

Laakso discloses an anthrapyrazole compound substituted at the 3-position with -CO₂Et. Amended claim 1 and composition claim 8, which depends from claim 1, do not encompass compounds substituted at the 3-position with an ester. Amended claim 2 does not encompass compounds substituted at the 3-position with an ester. The compound of composition claim 24 is unsubstituted. The compounds of amended claim 25 are not substituted at the 3-position. Claim 50 depends from both composition claim 24 which recites unsubstituted compounds and composition claim 34 which is not rejected under 35 U.S.C. § 102(b). Accordingly, none of claims 1, 2, 8, 24, 25 or 50 read on a compound of Laakso.

Mosby discloses an anthrapyrazole compound substituted at the 3-position with -NO₂. Amended claim 1 and composition claim 8, which depends from claim 1, do not encompass compounds substituted at the 3-position with -NO₂. Amended claim 2 does not encompass compounds substituted at the 3-position with -NO₂. The compound of composition claim 24 is unsubstituted. The compounds of amended claim 25 are not substituted at the 3-position. Claim 50 depends from both composition claim 24 which recites unsubstituted compounds and composition claim 34 which is not rejected under 35 U.S.C. § 102(b). Accordingly, none of claims 1, 2, 8, 24, 25 or 50 read on a compound of Mosby.

Akamatsu discloses anthrapyrazole compounds substituted at the 8-position with -NH₂ or -NO₂. Amended claim 1 and composition claim 8, which depends from claim 1, do not encompass compounds substituted at the 8-position with -NH₂ or -NO₂. Amended claim 2 does not encompass compounds substituted at the 8-position with -NH₂ or -NO₂. The compound of composition claim 24 is unsubstituted. The compounds of amended claim 25 are not substituted at the 8-position with -NH₂ or -NO₂. Claim 50 depends from both composition claim 24 which recites unsubstituted compounds and composition claim 34 which is not rejected under 35 U.S.C. § 102(b). Accordingly, none of claims 1, 2, 8, 24, 25 or 50 read on a compound of Akamatsu.

The compound of Example 12, column 4 of Tzikas I is unsubstituted. The compounds recited in pending claims 1, 2, 8 and 25 require substituents. Claims 24 and 50 are directed to pharmaceutical compositions. Tzikas I teaches that the compounds disclosed therein are used as starting materials for the synthesis of vat dyes (see Tzikas, column 1, lines 64-65). Tzikas I does not disclose any pharmaceutical compositions, let alone a pharmaceutical composition comprising a compound encompassed by pharmaceutical composition claims 24 or 50. Accordingly, none of claims 1, 2, 8 or 25 read on a compound

of Tzikas I and Tzikas I does not recite a pharmaceutical composition of claim 24 or claim 50.

Hoechst and Neeff each disclose anthrapyrazole compounds substituted at the 5- or 8-position with -NH₂. Amended claim 1 and composition claim 8, which depends from claim 1, do not encompass compounds substituted at the 5- or 8-position with -NH₂. Amended claim 2 does not encompass compounds substituted at the 5- or 8-position with -NH₂. The compound of composition claim 24 is unsubstituted. The compounds of amended claim 25 are not substituted at the 5- or 8-position with -NH₂. Claim 50 depends from both composition claim 24 which recites unsubstituted compounds and composition claim 34 which is not rejected under 35 U.S.C. § 102(b). Accordingly, none of claims 1, 2, 8, 24, 25 or 50 read on a compound of Hoechst or Neeff.

To summarize, compound claims 1, 2 and 25 as amended do not read on any compound of Laakso, Mosby, Akamatsu, Tzikas I, Hoechst or Neeff. Composition claim 8 depends from claim 1 and, accordingly, does not read on any compound of Laakso, Mosby, Akamatsu, Tzikas I, Hoechst or Neeff. The only reference which discloses an unsubstituted anthrapyrazole is Tzikas I, which does not disclose a pharmaceutical composition and, accordingly, cannot anticipate claim 24. Thus, none of Laakso, Mosby, Akamatsu, Tzikas I, Hoechst or Neeff. anticipates composition claim 24. Composition claim 50 depends from composition claim 24 and unrejected composition claim 34 and, accordingly, is not anticipated by Laakso, Mosby, Akamatsu, Tzikas I, Hoechst or Neeff..

Accordingly, in view of the above amendments and remarks, Applicants respectfully submit that the rejection of claims 1, 2, 8, 24, 25 and 50 under 35 U.S.C. § 102(b) has been overcome and must be withdrawn.

III. The Rejection Under 35 U.S.C. § 103(a)

Claims 2, 3, 26, 27, 52 and 54 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 4,198,518 to Tzikas (“Tzikas II”) and U.S. Patent No. 4,556,654 to Showalter *et al.* (“Showalter”), each taken alone.

To establish a *prima facie* case of obviousness there must be some suggestion or motivation, either in the cited reference or generally known to one of ordinary skill in the art, to modify the reference to arrive at the claimed compounds and there must also be a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Tzikas II discloses monosubstituted anthrapyrazole compounds substituted at the 3-position with C₁-C₆ alkyl, C₁-C₆ alkoxy or COR which are useful as intermediates for the production of vat dyes, pigments and disperse dyes (see Tzikas II, column 2, lines 3-5). None of claims 2, 26, 27 or 54 recite compounds substituted at the 3-position with the substituents recited in Tzikas II. Claims 3 and 52 recite compounds with at least two substituents, which Tzikas II does not disclose or suggest. Applicants submit that there is no suggestion or motivation found in Tzikas II to modify the vat dyes, pigments and disperse dyes disclosed therein to arrive at the compounds of claims 2, 3, 26, 27, 52 and 54 which are useful as therapeutic agents.

The Federal Circuit has held that in obviousness rejections based on close similarity in chemical structure, the necessary motivation to make a claimed compound, and thus the *prima facie* case of obviousness, rises from the expectation that the compounds similar in structure will have similar properties. *In re Lalu*, 747 F.2d 703, 706 (Fed. Cir. 1984). In view of the fact that Tzikas II teaches that the compounds disclosed therein are useful as industrial agents, Applicants submit that Tzikas II does not provide the requisite motivation to make the claimed compounds and cannot provide a reasonable expectation of success with respect to modifying the disclosed industrial agents to arrive at safe and effective therapeutic agents. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Showalter discloses anthrapyrazole compounds substituted at the 5-position with a substituted or unsubstituted amino group and also optionally having certain substituents at the 7-, 8-, 9- and 10-positions. In addition, the overwhelming majority of individual compounds disclosed by Showalter are substituted at the N-2 position. The compounds of Showalter are disclosed as being antibiotics, antifungal agents, having antileukemic activity and having activity *in vitro* activity against human colon adenocarcinoma cells. The compounds of claims 2, 3, 26, 27, 52 and 54 are characterized by being unsubstituted at the N-2 position and are useful for treating certain diseases including, but not limited to, cancer.

It is well established that the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992). Rather, a finding of obviousness requires that the prior art reference disclosing the generic formula must also provide the requisite motivation to arrive at the claimed compounds, wherein the Federal Circuit has held that the properties taught by the prior art references to be possessed by the compounds are relevant to determining if the requisite motivation is present. *In re Lalu*, 747 F.2d 703, 706 (Fed. Cir. 1984). Furthermore, the Federal Circuit has held that the disclosure of a chemical genus does not render obvious

any compound falling within the genus, particularly when the disclosure indicates a preference leading away from the claimed compounds. *In re Baird*, 16 F.3d 380, 382-383 (Fed. Cir. 1994).

When determining whether one of ordinary skill in the art would have been motivated to select particular species or a particular subgenus to arrive at the claimed compounds, the Examiner should consider *inter alia* the teachings of structural similarity (*i.e.*, which species or subgenus are described as typical, preferred or optimum). See MPEP 2144.08. In doing so, any teaching or suggestion of a preferred species or subgenus that is structurally different from the claimed species or subgenus may weigh against selecting the claimed species or subgenus and, accordingly, against a determination of obviousness. *In re Baird*, 16 F.3d at 382-383; MPEP 2144.08. Applicants respectfully submit that the compounds of claims 2, 3, 26, 27, 52 and 54 are not obvious in view of the disclosure of Showalter and that the disclosure of Showalter, in fact, leads one away from these compounds.

The overwhelming majority of individual compounds disclosed in Showalter as being useful for treating tumors are N-2 substituted compounds. In contrast, the compounds of the present invention are characterized by being unsubstituted at the N-2 position. Showalter discloses data for over 50 compounds from an *in vivo* lymphocytic leukemia P388 assay (see Showalter, column 28, line 56 to column 35, line 5), none of which are unsubstituted at the N-2 position. Showalter discloses *in vitro* data for three compounds against L1210 leukemia cells and *in vitro* data for one compound against multiple tumor cell lines (see Showalter, column 35), none of which are unsubstituted at the N-2 position. Showalter discloses *in vitro* data for over 40 compounds against human colon adenocarcinoma cells (see Showalter, column 38 to column 39), only one of which is unsubstituted at the N-2 position (see Showalter, column 38, 4th compound). Furthermore, a comparison of the ID₅₀ value for the single N-2 unsubstituted compound to that of compound which is identical except for being -CH₃ substituted at the N-2 position (see Showalter, column 38, 5th compound) reveals that addition of the -CH₃ substituent at this position increases the antitumor activity by over an order of magnitude (*i.e.*, 1.5×10^{-6} for N-2 unsubstituted compared to 4.0×10^{-7} for N-2 -CH₃ substituted). Applicants submit that the testing of only a single N-2 unsubstituted compound out of approximately 100 total compounds tested, especially in view of the fact that the unsubstituted compound tested was more than ten times less active solely due to the lack of an N-2 substituent, clearly shows that N-2 substituted compounds are the preferred compounds of Showalter. Applicants further submit that this disclosure evidences the fact that Showalter lacks the motivation to arrive at the compounds of claims 2, 3, 26, 27, 52 and

54 (*i.e.*, N-2 substituted compounds) from the class of compounds disclosed therein as required for a finding of obviousness. *In re Lahu*, 747 F.2d 703, 705 (Fed. Cir. 1984).

Accordingly, in view of the above, Applicants respectfully submit that the rejection of claims 2, 3, 26, 27, 52 and 54 under 35 U.S.C. § 103(a) has been overcome and must be withdrawn.

IV. Objection to claims 4-7, 34, 35, 38, 47-49, 51 and 53

Claims 4-7, 34, 35, 38, 47-49, 51 and 53 are objected to as being dependent upon a rejected base claim. Applicants respectfully submit that all presently pending claims are in condition for allowance in view of the above amendments and remarks and that the objection to claims 4-7, 34, 35, 38, 47-49, 51 and 53 must be withdrawn.

V. Conclusion

Applicants respectfully submit that all of the pending claims are now in condition for allowance. If the Examiner still disagrees, she is invited to call the undersigned to schedule an interview to resolve any remaining concerns.

It is believed that no fee is due in connection with this Reply on than that for the extension of time; however, in the event any additional fee is required, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Anthony M. Insogna, Reg. No. 35,203

Date January 4, 2005

By: Michel J. Brunni, Reg. No. 47,458 35,203

Anthony M. Insogna (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(858) 314-1130